Answer 1:

Bibliographic Information

The novel melphalan prodrug J1 inhibits neuroblastoma growth in vitro and in vivo. Wickstroem, Malin; Johnsen, John Inge; Ponthan, Frida; Segerstroem, Lova; Sveinbjoernsson, Baldur; Lindskog, Magnus; Loevborg, Henrik; Viktorsson, Kristina; Lewensohn, Rolf; Kogner, Per; Larsson, Rolf; Gullbo, Joachim. Division of Clinical Pharmacology, Department of Medical Sciences, Uppsala University, Uppsala, Swed. Molecular Cancer Therapeutics (2007), 6(9), 2409-2417. Publisher: American Association for Cancer Research, CODEN: MCTOCF ISSN: 1535-7163. Journal written in English. CAN 147:479966 AN 2007:1043798 CAPLUS

Abstract

Neuroblastoma is the most common extracranial solid tumor of childhood. The activity of J1 (L-melphalanyl-p-L-fluorophenylalanine Et ester), an enzymically activated melphalan prodrug, was evaluated in neuroblastoma models in vitro and in vivo. Seven neuroblastoma cell lines with various levels of drug resistance were screened for cytotoxicity of J1 alone or in combination with std. cytotoxic drugs, using a fluorometric cytotoxicity assay. J1 displayed high cytotoxic activity in vitro against all neuroblastoma cell lines, with IC50 values in the submicromolar range, significantly more potent than melphalan. The cytotoxicity of J1, but not melphalan, could be significantly inhibited by the aminopeptidase inhibitor bestatin. J1 induced caspase-3 cleavage and apoptotic morphol., had additive effects in combination with doxorubicin, cyclophosphamide, carboplatin, and vincristine, and synergistically killed otherwise drug-resistant cells when combined with etoposide. Athymic rats and mice carrying neuroblastoma xenografts [SH-SY5Y, SK-N-BE(2)] were treated with equimolar doses of melphalan, J1, or no drug, and effects on tumor growth and tissue morphol. were analyzed. Tumor growth in vivo was significantly inhibited by J1 compared with untreated controls. Compared with melphalan, J1 more effectively inhibited the growth of mice with SH-SY5Y xenografts, was assocd. with higher caspase-3 activation, fewer proliferating tumor cells, and significantly decreased mean vascular d. In conclusion, the melphalan prodrug J1 is highly active in models of neuroblastoma in vitro and in vivo, encouraging further clin. development in this patient group.

Answer 2:

Bibliographic Information

Antimyeloma effects of arsenic trioxide are enhanced by melphalan, bortezomib and ascorbic acid. Campbell, Richard A.; Sanchez, Eric; Steinberg, Jeffrey A.; Baritaki, Stavroula; Gordon, Melinda; Wang, Cathy; Shalitin, Dror; Chen, Haiming; Pang, Shen; Bonavida, Benjamin; Said, Jonathan; Berenson, James R. Institute for Myeloma & Bone Cancer Research, West Hollywood, The University of California, Los Angeles, CA, USA. British Journal of Haematology (2007), 138(4), 467-478. Publisher: Blackwell Publishing Ltd., CODEN: BJHEAL ISSN: 0007-1048. Journal written in English. CAN 147:479931 AN 2007:1032111 CAPLUS

Abstract

Arsenic trioxide (ATO) induces apoptosis of malignant plasma cells through multiple mechanisms, including inhibition of DNA binding by nuclear factor kappa-B, a key player in the development of chemoresistance in multiple myeloma (MM). This activity suggests that ATO may be synergistic when combined with other active antimyeloma drugs. To evaluate this, we examd. the antimyeloma effects of ATO alone and in combination with bortezomib, melphalan and ascorbic acid (AA) both in vitro and in vivo using a severe combined immunodeficient (SCID)-hu murine myeloma model. Marked synergistic antimyeloma effects were demonstrated when human MM Los Angeles xenograft IgG lambda light chain (LAGλ-1) cells were treated in vitro with ATO and any one of these agents. SCID mice bearing human MM LAGλ-1 tumors were treated with single-agent ATO, bortezomib, melphalan, or AA, or combinations of ATO with either bortezomib or melphalan and AA. Animals treated with any of these drugs alone showed tumor growth and increases in paraprotein levels similar to control mice, whereas animals treated with ATO-contg. combinations showed markedly suppressed tumor growth and significantly reduced serum paraprotein levels. These in vitro and in vivo results suggest that addn. of ATO to other antimyeloma agents may result in improved outcomes for patients with relapsed or refractory MM.

Answer 3:

Bibliographic Information

The Bcl-2 Family Protein Inhibitor, ABT-737, Has Substantial Antimyeloma Activity and Shows Synergistic Effect with Dexamethasone and Melphalan. Trudel, Suzanne; Stewart, A. Keith; Li, Zhihua; Shu, Yanjun; Liang, Sheng-Ben; Trieu, Young; Reece, Donna; Paterson, Josh; Wang, Dingyan; Wen, Xiao-Yan. Department of Medical Oncology and Hematology, Princess Margaret Hospital, University Health Network, Toronto, Can. Clinical Cancer Research (2007), 13(2, Pt. 1), 621-629. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 146:308645 AN 2007:87080 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Purpose: The aim of this study is to investigate the antimyeloma activity of a novel Bcl-2 family inhibitor, ABT-737, in preclin. treatment of multiple myeloma. Exptl. Design: The antimyeloma activity of ABT-737 was evaluated in cultured myeloma cell lines and patient myeloma samples, and in a xenograft mouse myeloma model. Drug combination therapy using ABT-737 with other commonly used myeloma drugs was also investigated. Results: MY5 and JJN3 cell lines exhibited the most sensitivity to ABT-737 with an EC50 of 0.2 and 0.5 μmol/L, resp., with increased cell apoptosis and elevated activated caspase-3. We identified two distinct groups of myeloma patient samples that were either sensitive or resistant to the drug. Four of 15 patient bone marrow samples (27%) were highly sensitive to ABT-737 at doses of 0.25 and 0.5 μmol/L, which eliminated 80% to 90% of myeloma cells as a result of cellular apoptosis 3 days after drug treatment. ABT-737 showed a synergistic effect when combined with dexamethasone or melphalan in inducing myeloma cell death. Furthermore, the dexamethasone-resistant MM1(Dex)R myeloma cell line was highly sensitive to 0.2 μmol/L ABT-737. As detd. by colony assay, little or no detectable toxicity to patient hematol. progenitor cells was obsd. at 1 μmol/L ABT-737. ABT-737 dose dependently suppressed tumor growth in a xenograft MY5 mouse model. Conclusions: These studies show substantial antimyeloma activity of ABT-737 as a single agent or in combination with dexamethasone or melphalan and suggest a rationale for future clin. trials.

Answer 4:

Bibliographic Information

Development of human lymphoma/leukemia xenograft models in immune-deficient mice for evaluation of potential anticancer agents. Dykes, D. J.; Hollingshead, M. G.; Camalier, R. F.; Waud, W. R.; Mayo, J. G. Southern Research Institute, Birmingham, AL, USA. Contributions to Oncology (1999), 54(Relevance of Tumor Models for Anticancer Drug Development), 295-304. Publisher: S. Karger AG, CODEN: COONEV ISSN: 0250-3220. Journal written in English. CAN 133:217399 AN 2000:242563 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Eleven human lymphoma/leukemia cell lines were assessed as in vivo xenograft models in severe combined immunodeficient (SCID) mice. In prepn. for efficacy evaluations of new antitumor agents, all eleven cell lines have been characterized for sensitivity to known clin. useful agents. The lines included in the study represent a variety of diseases including T-cell, myelogenous, and lymphoblastic leukemias, as well as histiocytic, B-cell and Burkitt's lymphomas. The selected agents for this study were representative of various chem. classes. Addnl., growth studies were performed including comparisons in athymic nude mice. These studies were designed to det. s.c. tumor vol. doubling times, graft success, latent growth periods, and other characteristics necessary to effectively implement and interpret anticancer efficacy evaluations. The various tumor lines used proved to be good models for chemotherapy trials. In the chemotherapy trials, considerable independent chemotherapeutic profiles were obsd. but there were also some similarities among the various histol. types.

Answer 5:

Bibliographic Information

Rapid development of drug resistance in human ovarian tumor xenografts after a single treatment with melphalan in vivo. Caffrey, Paula B.; Zhang, Yixin; Frenkel, Gerald D. Department of Biological Sciences, Rutgers University, Newark, NJ, USA. Anticancer Research (1998), 18(4C), 3021-3026. Publisher: Anticancer Research, CODEN: ANTRD4 ISSN: 0250-7005. Journal written in English. CAN 129:254570 AN 1998:559949 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Human ovarian tumors from A2780 cells were grown as xenografts in immunodeficient mice, treated with a single i.p. dose of melphalan and tumor cells were removed and placed into tissue culture. The cells from the treated tumors exhibited an approx. 2-fold resistance to melphalan in vitro compared to cells taken from untreated tumors. This degree of resistance was similar to that of cells from tumors formed from melphalan-resistant A2780-ME cells. The cells from the treated tumors were also resistant to cisplatin but not to doxorubicin. They contained approx. 2- fold higher levels of glutathione than cells from the untreated tumors. Exposure of the cells to buthionine sulfoximine (a specific inhibitor of glutathione biosynthesis) eliminated the difference in glutathione levels as well as the difference in sensitivity to melphalan. When tumor-bearing animals were treated with buthionine sulfoximine in addn. to melphalan the resulting tumor cells were not resistant to the drug. Resistance could also be demonstrated in the tumors themselves in vivo: the growth of previously untreated tumors was severely inhibited by a high dose of melphalan (11.7mg/kg) administered i.p. to the animals, whereas the growth of tumors which had received prior treatment with melphalan was unaffected by the subsequent high dose. The rapid development of drug-resistant tumor cells after a single drug treatment in vivo makes this an excellent system for the investigation of the mechanisms by which resistance develops as well as for use in the screening for agents which can prevent it.

Answer 6:

Bibliographic Information

Treatment of human ovarian tumor xenografts with selenite prevents the melphalan-induced development of drug resistance. Caffrey, Paula B.; Frenkel, Gerald D. Department of Biological Sciences, Rutgers University, Newark, NJ, USA. Anticancer Research (1998), 18(4C), 3017-3020. Publisher: Anticancer Research, CODEN: ANTRD4 ISSN: 0250-7005. Journal written in English. CAN 129:254569 AN 1998:559948 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Human ovarian tumors (derived from A2780 cells), growing as s.c. xenografts in immunodeficient mice, develop melphalan-resistant cells after a single treatment of the tumor-bearing animal with the drug [Caffrey, Zhang and Frenkel, submitted for publication]. Treatment of the animals with selenite by i.p. injection prevented the development of primary resistance to melphalan as well as cross-resistance to cisplatin. Selenite treatment also prevented the melphalan-induced increase in the cellular level of glutathione. In contrast, selenite administered s.c. or in drinking water had relatively little effect on the development of resistance. The results in this animal model suggest that selenite may be clin. useful in preventing the development of drug resistance during chemotherapy of cancer.

Answer 7:

Bibliographic Information

Prostate carcinoma response to cytotoxic therapy: in vivo resistance. Teicher, Beverly A.; Kakeji, Yoshihiko; Ara, Gulshan; Herbst, Roy S.; Northey, David. Dana-Farber Cancer Institute and Joint Center for Radiation Therapy, Boston, MA, USA. In Vivo (1997), 11(6), 453-462. Publisher: International Institute of Anticancer Research, CODEN: IVIVE4 ISSN: 0258-851X. Journal written in English. CAN 128:252636 AN 1998:145193 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Androgen independent prostate cancer is recognized as a chemotherapy resistant disease. Human prostate carcinoma DU-145,

LNCaP and PC-3 cells in monolayer in exponential growth were exposed to various concns. of melphalan, 4-hydroperoxycyclophosphamide or adriamycin for 1 h. These cells were all responsive to the drugs, with DU-145 cells being the least sensitive and PC-3 cells the most sensitive. When the three human prostate carcinoma cell lines were grown as xenografts in nude or SCID mice and the animals treated with single doses of melphalan, cyclophosphamide or adriamycin, the tumors were not very responsive to the drugs. The DU-145 tumors were highly resistant to each drug. The PC-3 tumors were more sensitive; however, even the PC-3 tumors were less drug responsive than several murine tumors. All three prostate cell lines secreted transforming growth factor-β (TGF-β) into the cell culture medium, and when grown as xenograft tumors increased the plasma levels of TGF-β in the animals. DU-145 cells produced the most TGF-β and LNCaP cells produced the least. After administration of single doses of each of the chemotherapeutic agents to animals bearing the prostate carcinoma xenografts, there was a time dependent increase in plasma TGF-β that was greatest in animals bearing the DU-145 tumor and least in animals bearing the LNCaP tumor. Immunohistochem. staining, showed that PC-3 tumors tended to have the most intense staining for TGF-β and LNCaP tumors the least. In situ hybridization for TGF-β mRNA showed an increase in TGF-β mRNA that was time independent after chemotherapy administration in all three tumors. These results support the hypothesis that the drug resistance of prostate carcinoma is manifest in vivo, and that in vivo high levels of TGF-β may protect these tumors from cytotoxic cancer therapies.

Answer 8:

Bibliographic Information

Lack of antitumor activity of human recombinant tumor necrosis factor-α, alone or in combination with melphalan in a nude mouse human melanoma xenograft system. Furrer, Markus; Altermatt, Hans Jorg; Ris, Hans Beat; Althaus, Ulrich; Ruegg, Curzio; Lienard, Danielle; Lejeune, Ferdy J. Department of Thoracic and Cardiovascular Surgery, University of Bern, Switz. Melanoma Research (1997), 7(Suppl. 2), S43-S49. Publisher: Rapid Science Publishers, CODEN: MREEEH ISSN: 0960-8931. Journal written in English. CAN 128:33596 AN 1997:749113 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The most promising developments in the field of isolated limb perfusion have centered around the use of the recombinant cytokine tumor necrosis factor-α (rTNF-α) in combination with melphalan. While the results of clin. trials are impressive, the exact antitumor mechanisms of rTNF-α and its role in combination with melphalan remain unclear. Our aim was to study the antitumor activity of human rTNF-α with or without the combination of melphalan in a nude mouse human melanoma xenograft system. In a first attempt to define the maximal tolerated single dose of rTNF-α in this setting, 15 animals were exposed to increasing doses of rTNF-α (60-2500 μg/kg i.p.). All but one animal survived and tumor growth was not influenced by these single dose applications of rTNF-α even at the very high doses. Anti-tumor activity of repeated application of melphalan (three times 9 μg/kg in group 2 and three times 6 mg/kg in group 3), of rTNF-α alone (nine doses of 50 μg/kg in group 4), and of rTNF-α in combination with melphalan (nine doses of 50 μg/kg rTNF-α and three times 6 mg/kg melphalan in group 5) was further compared with non-treated animals (group 1). Tumor growth was significantly inhibited in all animals treated with melphalan (group 2, 3 and 5), but was not decreased in animals treated with rTNF-α alone (group 4). Mean final tumor vols. and mean tumor wt. were not different in group 2 (789 mm3, 0.38 g), group 3 (1173 mm3, 0.55 g) and group 5 (230 mm3, 0.37 g), but significantly lower than group 1 (3156 mm3, 2.35 g) and group 4 (3228 mm3, 2.00 g). There were no significant differences between high and low dose melphalan treatment and between melphalan treatment in combination with rTNF-α. Histol. examn. did not show differences between treated and non-treated animals besides slightly inhibited mitotic activities of tumor cells in melphalan-treated animals. While tumor growth of human xenotransplanted melanoma in nude mice could be inhibited by melphalan, we failed to demonstrate any antitumor effect of rTNF-α.

The combination of melphalan and rTNF-α did not enhance the antiproliferative effect of melphalan alone. Human xenotransplanted tumors on nude mice might not be the ideal exptl. setting for studies of potential direct antineoplastic activity of rTNF-α, and these results support the concept that TNF-α exerts its antitumor activity indirectly, possibly by impairing the tumor vasculature and by activating the immune system.

Answer 9:

Bibliographic Information

L-Amino acid oxidase (LOX) modulation of melphalan activity against intracranial glioma. Moynihan, Kate; Elion, Gertrude

B.; Pegram, Charles; Reist, Craig J.; Wellner, Daniel; Bigner, Darell D.; Griffith, Owen W.; Friedman, Henry S. Medical Center, Duke Univ., Durham, NC, USA. Cancer Chemotherapy and Pharmacology (1997), 39(3), 179-186. Publisher: Springer, CODEN: CCPHDZ ISSN: 0344-5704. Journal written in English. CAN 127:426 AN 1997:262016 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The efficacy of pretreatment with L-amino acid oxidase (LOX) and LOX antiserum in the modulation of melphalan activity against intracranial glioma was evaluated. LOX depleted the large neutral amino acids Ile, Leu, Met, Phe, Tyr, and Val in murine blood plasma at doses of 100-200 μg. Anti-LOX serum inhibited .apprx.50% of LOX activity in vitro. Anti-LOX serum prevented LOX-mediated catabolism of melphalan in vivo. Inoculation of anti-LOX serum after treatment with 100 μg LOX reduced LOX activity by 100, 89, and 100% at 6 h compared with redns. of 80, 59, and 52% over the same period in animals receiving LOX alone. In mice bearing intracranial human glioma xenografts, pretreatment with LOX followed by anti-LOX serum increased antitumor activity of melphalan.

Answer 10:

Bibliographic Information

Enhancement of melphalan activity by inhibition of DNA polymerase-α and DNA polymerase-β Moynihan, Kate; Elion, Gertrude B.; Ali-Osman, Francis; Marcelli, Susan; Keir, Stephen; Bigner, Darell D.; Friedman, Henry S. Medical Center, Duke University, Durham, NC, USA. Cancer Chemotherapy and Pharmacology (1996), 38(4), 349-354. Publisher: Springer, CODEN: CCPHDZ ISSN: 0344-5704. Journal written in English. CAN 125:212094 AN 1996:520804 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The alteration of melphalan (I) activity in s.c. human rhabdomyosarcoma xenografts TE-671 and TE-671 MR in mice was investigated after inhibition of DNA polymerase-α using aphidicolin glycinate (II) and DNA polymerase-β using dideoxycytidine (III). II (90 mg/m2) enhanced the activity of I against TE-671, with growth delays increasing by 8.4, 15.8, and 21.2 days over the regimen with I only. II (180 mg/m2) only modestly increased I activity against TE-671 MR, with the growth delays increasing from 9.6 and 12.1 days using I alone to 12.1 and 14.5 days using I plus II. II (180 mg/m2) plus I produced greater wt. loss compared with I alone. II plus O6-benzylguanine did not increase the activity of 1,3-bis(2-chloroethyl)-1-nitrosourea against TE-671 or TE-671 MR. II (90 and 180 mg/m2) inhibited DNA polymerase-α to 80 and 72% in TE-671 and 64 and 37% in TE-671-MR, and III inhibited DNA polymerase-β to 59% in TE-671 and 48% in TE 671-MR. A role for II-mediated enhancement of I activity in the treatment of newly diagnosed I-sensitive tumors is suggested.

Answer 11:

Bibliographic Information

Isoenzyme-specific glutathione S-transferase inhibitors potentiate drug sensitivity in cultured human tumor cell lines. Morgan, Amy S.; Ciaccio, Paul J.; Tew, Kenneth D.; Kauvar, Lawrence M. Terrapin Technologies Inc., South San Francisco, CA, USA. Cancer Chemotherapy and Pharmacology (1996), 37(4), 363-70. Publisher: Springer, CODEN: CCPHDZ ISSN: 0344-5704. Journal written in English. CAN 124:250058 AN 1996:160265 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Novel glutathione (GSH) analogs, previously shown to inhibit glutathione S-transferase (GST) activity at about 1 μM in vitro, were tested for their ability to potentiate the killing of cultured tumor cells by chemotherapeutic drugs. When tested at doses up to 200 μM, the analogs were neither toxic nor capable of potentiating drug toxicity unless the di-Et ester (DEE) form was used for treatment of the cells. HPLC anal. revealed rapid internalization of the DEE and intracellular conversion to a monoethyl ester form that accumulated in

the cell, followed by a more gradual loss of the second ester to generate the active parent form. For the four GSH analogs tested, the ability of the DEE forms to potentiate chlorambucil (CMB) toxicity in HT-29 human colon adenocarcinoma cells strongly correlated with the in vitro ability of the parent form to inhibit recombinant human P1-1. This isoenzyme is the dominant form of GST present in HT-29 cells. Of the four analog DEEs tested, γ-glutamyl-S-(benzyl)cysteinyl-R(-)-Ph glycine (TER 117) DEE was the most effective in potentiating CMB toxicity in several cell lines: HT-29, HT4-1 (HT-29 subclone), SKOV-3 ovarian carcinoma, and SK VLB (vinblastine-resistant variant of SKOV-3) cells. γ-Glutamyl-S-(octyl)cysteinyl-glycine (TER 143) DEE potentiated mitomycin C (MTC) toxicity in HT4-1 and SK VLB cells while TER 117 DEE did not. TER 117 DEE enhanced melphalan effects on xenografts of HT4-1 in mice to a similar extent as that achieved with the previously described nonspecific GST inhibitor, ethacrynic acid. Our results indicate that cell-permeable analogs of GSH can potentiate cytotoxicity of common chemotherapeutic drugs and this effect has a strong pos. correlation with the ability of the analogs to inhibit specific GST isoenzymes.

Answer 12:

Bibliographic Information

The effect of L-amino acid oxidase on activity of melphalan against an intracranial [glioma] xenograft. Rich, Jeremy N.; Elion, Gertrude B.; Wellner, Daniel; Colvin, O. Michael; Groothuis, Dennis R.; Hilton, John H.; Schlageter, Kurt E.; Bigner, Darell D.; Griffith, Owen W.; Friedman, Henry S. Department Medicine, Johns Hopkins Hospital, Baltimore, MD, USA. Cancer Chemotherapy and Pharmacology (1995), 36(5), 379-84. Publisher: Springer, CODEN: CCPHDZ ISSN: 0344-5704. Journal written in English. CAN 123:306017 AN 1995:872799 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

It was previously shown that diet restriction-induced depletion of large neutral amino acids (LNAAs) in murine plasma to 46% of control levels enhances the intracranial delivery of melphalan without enhancing delivery to other organs. Studies were now conducted to det. whether more substantial LNAA depletion could further enhance intracranial delivery of melphalan. Treatment with L-amino acid oxidase (LOX) depleted murine plasma LNAAs: phenylalanine, leucine, and tyrosine (>95%); methionine (83%); isoleucine (70%); and valine (46%). Expts. evaluating the intracellular uptake of melphalan and HPLC quantitation of melphalan metabolites revealed, however, that melphalan is rapidly degraded in the presence of LOX, and that the timing of the administration of melphalan following the use of LOX to deplete LNAAs is crucial. Conditions were found under which LOX-mediated degrdn. of melphalan was minimized and LNAA depletion was maximized, resulting in a potentiation of the antitumor effect of melphalan on human glioma xenografts in nude mice. Such potentiation could not be obtained by using diet restriction alone.

Answer 13:

Bibliographic Information

Flunarizine enhancement of melphalan activity against drug-sensitive/resistant rhabdomyosarcoma. Castellino, SM; Friedman, HS; Elion, GB; Ong, ET; Marcelli, SL; Page, R; Bigner, DD; Dewhirst, MW. Medical Center, Duke University, Durham, NC, USA. British Journal of Cancer (1995), 71(6), 1181-7. CODEN: BJCAAI ISSN: 0007-0920. Journal written in English. CAN 123:132165 AN 1995:674432 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Flunarizine was tested for its ability to modulate either cyclophosphamide- or melphalan-induced growth delay of a drug-resistant rhabdomyosarcoma xenograft (TE-671 MR) in nude mice and the drug-sensitive parent line (TE-671), in which P-glycoprotein is not involved in the mechanism of drug resistance. Tumor blood flow was increased by 30% after a flunarizine dose of 4 mg/kg, but no modification in growth delay was induced by melphalan (12 mg/kg). In contrast, a 60-mg/kg dose of flunarizine had no effect on tumor blood flow, but the same dose enhanced melphalan-induced tumor regrowth delay in both tumor lines. The dose-modifying factor for flunarizine as an adjuvant to melphalan was approx. 2 for both tumor lines. Although blood flow measurements were not performed with the combination of flunarizine and melphalan, the results with flunarizine alone suggested that the augmentation of melphalan cytotoxicity is not mediated by changes in blood flow. In contrast, flunarizine did not affect drug sensitivity to cyclophosphamide in

animals bearing the drug-sensitive parent tumor line. These results suggest that the mechanism of drug sensitivity modification by flunarizine is not related to modification of tumor blood flow, but may be mediated by modification of transport mechanisms that are differentially responsible for cellular uptake and retention of melphalan as compared with cyclophosphamide.

Answer 14:

Bibliographic Information

Hyperthermia-induced enhancement of melphalan activity against a melphalan-resistant human rhabdomyosarcoma xenograft. Laskowitz, Daniel T.; Elion, Gertrude b.; Dewhirst, Mark W.; Griffith, Owen W.; Savina, Paul M.; Blum, M. Robert; Prescott, Deborah M.; Bigner, Darell D.; Friedman, Henry S. Med. Cent., Duke Univ., Durham, NC, USA. Radiation Research (1992), 129(2), 218-23. CODEN: RAREAE ISSN: 0033-7587. Journal written in English. CAN 118:116287 AN 1993:116287 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The effects of regional hyperthermia (42° for 70 min) on the antitumor activity of melphalan were examd. in athymic mice bearing melphalan-resistant rhabdomyosarcoma (TE-671 MR) xenografts growing in the right hind limb, and results were compared with similar studies of melphalan-sensitive (TE-671) parent xenografts. Melphalan alone at a dose of 36 mg/m2 (0.5 of the 10% LD) produced growth delays of 4.1 to 10.2 days in TE-671 MR xenografts and 21.8 to 28.7 days in TE-671, resp. Hyperthermia alone produced growth delays of 0.9 days in TE-671 MR xenografts and 0.8 days in TE-671. Combination therapy with malphalan and hyperthermia produced growth delays of 7.2 to 13.3 days in TE-671 MR xenografts and 34.3 and 42.8 days in TE-671, resp., representing a mean thermal enhancement ratio of 1.7 in TE-671 MR and 1.5 in TE-671. Measurement of glutathione levels in TE-671 MR xenografts following treatment with melphalan, hyperthermia, or melphalan plus hyperthermia revealed significant redns. in glutathione content with the nadir (60% of control values) seen 6 h following treatment. Glutathione levels in TE-671 xenografts followed identical therapy revealed no differences from control values. Hyperthermia plus melphalan did not result in a higher tumor-to-plasma melphalan ratio compared with treatment with malphalan alone in either TE-671 MR or TE-671 xenografts. These studies suggest that heat-induced alterations in tumor glutathione or malphalan levels are not responsible for the increase in melphalan activity produced by hyperthermia. Combination therapy with melphalan plus regional hyperthermia offers promise for treatment of melphalan-resistant neoplasms.

Answer 15:

Bibliographic Information

The effect of an amino acid-lowering diet on the rate of melphalan entry into brain and xenotransplanted glioma. Groothuis, Dennis R.; Lippitz, Bodo E.; Fekete, Istvan; Schlageter, Kurt E.; Molnar, Peter; Colvin, O. Michael; Roe, Charles R.; Bigner, Darell D.; Friedman, Henry S. Med. Sch., Northwestern Univ., Evanston, IL, USA. Cancer Research (1992), 52(20), 5590-6. CODEN: CNREA8 ISSN: 0008-5472. Journal written in English. CAN 118:15795 AN 1993:15795 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Melphalan (L-phenylalanine mustard, L-PAM, alkeran; mol. wt., 305,000) is transported across tumor cell membranes and the blood-brain barrier by the large neutral amino acid (LNAA) transport system. Normally, plasma LNAA levels are high enough and the affinity low enough that this system does not transport much melphalan into the brain. However, plasma amino acids can be reduced by fasting and protein-free diet. We used this method to reduce competition and to increase melphalan transport into brain tumors. In nude mice fasted for 12 h and then fed a protein-free diet for 2 and 6 h, mean plasma LNAA levels were 46% and 42% of control values. Nude mice with xenotransplanted D-45MG human gliomas were used to study tissue distribution and uptake kinetics of [3H]melphalan in a control group and a diet group (after a 12-h fast and 2 h of a 0% protein diet). The K1 (blood-to-tissue transfer const.) of melphalan, detd. by graphical anal. and by nonlinear fitting to a 2-compartment model, was higher in the diet group in all tumor regions except the necrotic center of s.c. tumors; the increase was significant in the tumor periphery of brain and s.c. tumors.

The ratio of K1s (diet to control) varied from 1.2 to 1.3 in brain tumors, 1.9 to 2.1 in s.c. tumors, and 1.8 to 3.1 in tumor-free brain. The apparent [3H]melphalan distribution space was significantly higher in the tumor periphery of both brain and s.c. tumors of the 15- and 30-min diet group. We also measured blood-brain barrier transport of [α-14C]aminoisobutyric acid and blood flow (with [131I]iodoantipyrine): the K1 of [α-14C]aminoisobutyric acid was 28.1 ± 6.6 (SE) in brain tumors and 24.3 ± 8.9 μL/g/min in s.c. tumors. Blood flow was 58.2 → 3.9 in brain tumors and 5.2 ± 0.4 mL/100 g/min in s.c. tumors. Fasting, when combined with a protein-free diet, reduces plasma amino acid levels and thereby reduces competition between melphalan and LNAAs. This may increase the amt.
of melphalan that can enter a brain tumor without increasing the administered drug dose and suggests a therapeutic manipulation that can be used to increase the delivery of melphalan.

Answer 16:

Bibliographic Information

Enhancement of melphalan-induced gastrointestinal toxicity in mice treated with regional hyperthermia and BSO-mediated glutathione depletion. Laskowitz, D. T.; Elion, G. B.; Dewhirst, M. W.; Griffith, O. W.; Cattley, R. C.; Bigner, D. D.; Friedman, H. S. Med. Cent., Duke Univ., Durham, NC, USA. International Journal of Hyperthermia (1992), 8(1), 111-20. CODEN: IJHYEQ ISSN: 0265-6736. Journal written in English. CAN 116:207425 AN 1992:207425 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Both hyperthermia and glutathione depletion have been shown to increase the antineoplastic activity of melphalan. Investigations were carried out to define the toxicity and activity of melphalan given in conjunction with local (right hind limb) hyperthermia and L-buthionine-SR-sulfoximine (BSO)-mediated glutathione depletion to athymic mice bearing the melphalan-resistant human rhabdomyosarcoma xenograft TE-671 MR. Administration of 0.5 of the 10% LD of melphalan to mice treated with BSO and hyperthermia (42° for 70 min) resulted in a 53% mortality rate. The mortality rates for mice treated with melphalan alone (2.5%), hyperthermia alone (0%), melphalan plus BSO (13.5%), melphalan plus hyperthermia (12.0%), and BSO plus hyperthermia (0%) were substantially lower than triple therapy. Histol. examn. of kidney, liver, colon, and small intestine sections taken from non-tumor-bearing animals revealed a marked increase in damage to the small intestine (cryptal necrosis and epithelial denudement) in animals receiving triple therapy compared with animals receiving any other treatment combination. Gavage administration of sterile, water (1 mL twice a day) completely prevented mortality in animals receiving triple therapy. Treatment of tumor-bearing animals with triple therapy plus gavage demonstrated a statistically significant increase in tumor growth delay compared with animals receiving any other treatment combination.

Answer 17:

Bibliographic Information

Reversal of melphalan resistance in vivo and in vitro by modulation of glutathione metabolism. Medh, Rheem D.; Gupta, Vicram; Awasthi, Yogesh C. Reg. Oncol. Cent., Mercy Hosp., Pittsburgh, PA, USA. Biochemical Pharmacology (1991), 42(2), 439-41. CODEN: BCPCA6 ISSN: 0006-2952. Journal written in English. CAN 115:149872 AN 1991:549872 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Melphalan-sensitive (Mels), -resistant (MelR) and -revertant (MelRev) HS-SuHan human myeloma cells were maintained in culture and as xenografts in nude mice. MelR tumors exhibited 1.8 fold higher glutathione S-transferase (GST) activity compared to MelS tumors; the MelRev tumors had intermediate values. Buthionine sulfoximine treatment of MelR cells and nude mice bearing MelR tumor resulted in 50-75% depletion of glutathione (GSH). GSH-depleted MelR tumors showed a rapid and almost complete regression by day 15 to melphalan in comparison to tumors whose GSH was not depleted. The data thus indicates that it is possible to overcome melphalan resistance in human myeloma cells by GSH depletion.

Answer 18:

Bibliographic Information

Melphalan-induced toxicity in nude mice following pretreatment with buthionine sulfoximine. Skapek, Stephen X.; VanDellen, Adrian F.; McMahon, Daniel P.; Postels, Douglas G.; Griffith, Owen W.; Bigner, Darell D.; Friedman, Henry S. Dep. Pediatr., Wilford Hall USAF Med. Cent., Lackland AFB, TX, USA. Cancer Chemotherapy and Pharmacology (1991), 28(1), 15-21. CODEN: CCPHDZ ISSN: 0344-5704. Journal written in English. CAN 115:41507 AN 1991:441507 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Melphalan-induced toxicity in nude mice following pretreatment with a regimen of L-buthionine sulfoximine (BSO), previously shown to enhance the activity of this alkylating agent against rhabdomyosarcoma and glioma xenografts, was examd. Mice were pretreated with i.p. BSO (2.5 mmol/kg × 7 doses as 12-h intervals plus concomitant availability of a 20-mM soln. in the drinking water) or vehicle prior to a single i.p. injection of melphalan (35.65 mg/m2). As compared with control animals who received no BSO pretreatment, mice pretreated with BSO lost wt. prior to therapy with melphalan (6.9% wt. loss vs 0.3% wt. gain) and showed a greater mean nadir wt. loss after melphalan (3.8% vs 2.1%). Treatment with melphalan was assocd. with histol. evidence of reversible gastrointestinal toxicity, reversible myelosuppression, and histol. evidence of acute renal tubular necrosis, with no differences being obsd. between mice that had been pretreated with BSO and those that had been pretreated with vehicle. No evidence of cardiac, hepatic, or skeletal muscle toxicity was found in melphalan-treated animals. These results suggest that treatment of nude mice with melphalan following BSO-mediated depletion of glutathione does not result in enhanced organ toxicity despite an increase in the antineoplastic activity of this alkylating agent.

Answer 19:

Bibliographic Information

Investigations on the antitumor effect and mutagenicity of α-MSH fragments containing melphalan. Suli-Vargha, H.; Jeney, A.; Kopper, L.; Olah, J.; Lapis, K.; Botyanszki, J.; Csukas, I.; Gyorvari, B.; Medzihradsky, K. Res. Group Pep. Chem., Hung. Acad. Sci., Budapest, Hung. Cancer Letters (Shannon, Ireland) (1990), 54(3), 157-62. CODEN: CALEDQ ISSN: 0304-3835. Journal written in English. CAN 114:156727 AN 1991:156727 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

α-MSH fragments contg. melphalan were tested in vivo on L1210 leukemia and on human amelanotic melanoma xenograft in mice and in vitro on human amelanotic melanoma cell lines. The compds. exhibit significant antitumor activity, but no selectivity in targeting of melanoma can be achieved. There is a difference between melphalan and the melphalyl-peptide in their action on protein synthesis. The peptide derivs. also are less mutagenic than melphalan, according to the SCE assay, furnishing further evidence for the pos. effect of natural carrier mols.

Answer 20:

Bibliographic Information

Establishment of a melphalan-resistant rhabdomyosarcoma xenograft with cross-resistance to vincristine and enhanced sensitivity following buthionine sulfoximine-mediated glutathione depletion. Rosenberg, Mindy C.; Colvin, O. Michael; Griffith, Owen W.; Bigner, Sandra H.; Elion, Gertrude B.; Horton, Julie K.; Lilley, Eileen; Bigner, Darell D.; Friedman, Henry S. Med. Cent., Duke Univ., Durham, NC, USA. Cancer Research (1989), 49(24, Pt. 1), 6917-22. CODEN: CNREA8 ISSN: 0008-5472. Journal written in English. CAN 112:69509 AN 1990:69509 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

A melphalan-resistant human rhabdomyosarcoma xenograft, TE-671 MR, was established in athymic mice by melphalan treatment of the parent xenograft, TE-671, at the 10% lethal dosage (LD10); resistance was evident after ten passages of the tumor. TE-671 MR demonstrated a doubling time of 3.5 days and a latency period to 1000-mm3 tumors of 27.5 days. The glutathione level of TE-671 MR was 2.36 μmol/g tumor, wet wt., 2-fold higher than the parent line. The glutathione S-transferase activity of TE-671 MR was 117.8 μmol/min/mg protein, essentially unchanged from the parent line. Although TE-671 MR demonstrated cross-resistance to vincristine, dot blot anal. did not reveal an elevated expression of mdr1 mRNA in the resistant line. TE-671 MR demonstrated a 9.7-day growth delay following treatment with melphalan at the LD10 (compared to 20.9 days for the parent line). Treatment with L-buthionine-SR-sulfoximine (BSO) resulted in increased sensitivity to melphalan subsequently administered at 50% of the LD10 (melphalan alone, growth delays of 3.7 and 4.6 days in duplicate trials; melphalan + BSO, growth delays of 7.2 and 9.8 days). Sensitivity to melphalan equal to that of the parent line TE-671 was not achieved, however. Treatment with BSO did not result in enhanced sensitivity to subsequently administered vincristine (50% of the LD10) (vincristine alone, growth delays of 6.8 and 6.9 days in duplicate trials; vincristine + BSO, growth delays of 10.9 and 7.5 days). These results suggest that generation of melphalan resistance may be assocd. with development of cross-resistance to vincristine; this resistance may be assocd. with (although not necessarily mediated by) glutathione elevation; this resistance may be partially overcome by BSO-mediated depletion of glutathione.

Answer 21:

Bibliographic Information

Increased melphalan activity in intracranial human medulloblastoma and glioma xenografts following buthionine sulfoximine-mediated glutathione depletion. Friedman, Henry S.; Colvin, O. Michael; Griffith, Owen W.; Lippitz, Bodo; Elion, Gertrude B.; Schold, S. Clifford, Jr.; Hilton, John; Bigner, Darell D. Med. Cent., Duke Univ., Durham, NC, USA. Journal of the National Cancer Institute (1989), 81(7), 524-7. CODEN: JNCIEQ ISSN: 0027-8874. Journal written in English. CAN 110:185541 AN 1989:185541 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Athymic BALB/c mice bearing intracranial human glioma (D-54 MG) or medulloblastoma (TE-671) xenografts were treated with melphalan alone or buthionine sulfoximine (BSO) followed by melphalan. BSO depleted intracellular glutathione to 7.5% of the control level. BSO plus melphalan increased median survival over that produced by melphalan alone: 45.3 vs. 26.4% in TE-671 and 69 vs. 27.6% in D-54 MG. The data justify modulation of chemotherapy and radiotherapy of primary malignant brain tumors by depletion of glutathione.

Answer 22:

Bibliographic Information

Melphalan transport, glutathione levels, and glutathione-S-transferase activity in human medulloblastoma. Friedman, Henry S.; Skapek, Stephen X.; Colvin, O. Michael; Elion, Gertrude B.; Blum, M. Robert; Savina, Paul M.; Hilton, John; Schold, S. Clifford, Jr.; Kurtzberg, Joanne; Bigner, Darell D. Duke Univ. Med. Cent., Durham, NC, USA. Cancer Research (1988), 48(19), 5397-402. CODEN: CNREA8 ISSN: 0008-5472. Journal written in English. CAN 109:163094 AN 1988:563094 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Melphalan transport, glutathione levels, and glutathione-S-transferase activity were measured in 2 continuous human medulloblastoma cell lines and transplantable xenografts in athymic nude mice, TE-671 and Daoy. In vitro mean glutathione levels were 10.06 nmol/106 cells in TE-671 and 2.96 nmol/106 cells in Daoy. In vitro mean glutathione-S-transferase values were 91.52 nmol/min/mg protein in TE-671 and 50.31 nmol/min/mg protein in Daoy. Transport studies revealed kinetic parameters of Km = 108.3 μM, Vmax = 363.1 pmol/106 cells/min in TE-671 and Km = 111.7 μM, Vmax = 180.6 pmol/106 cells/min in Daoy. Melphalan transport was inhibited by both

D,L-α-2-aminobicyclo[2.2.1]heptane-2-carboxylic acid and Na+ depletion in TE-671 and Daoy cells in vitro, indicating that both systems of amino acid transport are functional in these medulloblastoma lines. In vivo s.c. xenograft glutathione values were lower (7.79 nmol/mg protein) in TE-671 than in Daoy (13.68 nmol/mg protein). The mean plasma concn. in mice given a LD10 (71.3 mg/m2) of melphalan i.p. was 50.3 μM at 10 min, with the half-life of 29.9 min. At this dose, s.c. xenograft levels were 2-3-fold higher in TE-671 than in Daoy tumors for the 3-h period measured. These studies demonstrate transport parameters confirming facilitated transport of melphalan in human medulloblastoma, a mean murine plasma melphalan concn. (following treatment with melphalan) above the in vitro drug concn. at which there is a 90% redn. in the no. of colonies in comparison to controls for TE-671 and Daoy for 2 h, and glutathione and glutathione-S-transferase levels in the same range previously reported in other melphalan-sensitive and -resistant human tumors. Future work with spontaneous and acquired melphalan-resistant human medulloblastoma cell lines and xenografts will define the role of these mechanisms in mediating drug resistance.

Answer 23:

Bibliographic Information

Experimental chemotherapy of human medulloblastoma cell lines and transplantable xenografts with bifunctional alkylating agents. Friedman, Henry S.; Colvin, O. Michael; Skapek, Stephen X.; Ludeman, Susan M.; Elion, Gertrude B.; Schold, S. Clifford, Jr.; Jacobsen, Phillip F.; Muhlbaier, Lawrence H.; Bigner, Darell D. Med. Cent., Duke Univ., Durham, NC, USA. Cancer Research (1988), 48(15), 4189-95. CODEN: CNREA8 ISSN: 0008-5472. Journal written in English. CAN 109:142110 AN 1988:542110 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

A series of bifunctional alkylators were tested against the genotypically and phenotypically heterogeneous continuous human medulloblastoma cell lines TE-671, Daoy, and D283 Med in vitro and against TE-671 and Daoy growing as s.c. and intracranial xenografts in athymic mice. Drugs tested included melphalan, cyclophosphamide, iphosphamide, phenylketocyclophosphamide, thiotepa, 1,3-bis(2-chloroethyl)-1-nitrosourea (in vivo), and busulfan (in vivo). Melphalan and phenylketocyclophosphamide were the most active agents in vitro, with drug concns. at which there is a 90% redn. in the no. of colonies of 2.13, 5.29, and 4.72 μM for melphalan and 4.60, 5.01, and 4.34 μM for phenylketocyclophosphamide against TE-671, D283 Med, and Daoy, resp. Melphalan, cyclophosphamide, iphosphamide, phenylketocyclophosphamide, and thiotepa produced significant growth delays against s.c. TE-671 and Daoy xenografts, while no activity could be demonstrated for 1,3-bis(2-chloroethyl)-1-nitrosourea or busulfan. Melphalan, cyclophosphamide, iphosphamide, and thiotepa also produced significant increases in median survival in mice bearing intracranial TE-671 and Daoy xenografts. These results extend previous studies demonstrating the antitumor activity of N- and phosphoramide mustard-based bifunctional alkylating agents in the treatment of human medulloblastoma continuous cell lines and transplantable xenografts, and support the continued use of these agents in clin. trials.

Answer 24:

Bibliographic Information

Enhanced melphalan cytotoxicity following buthionine sulfoximine-mediated glutathione depletion in a human medulloblastoma xenograft in athymic mice. Skapek, Stephen X.; Colvin, O. Michael; Griffith, Owen W.; Elion, Gertrude B.; Bigner, Darell D.; Friedman, Henry S. Med. Cent., Duke Univ., Durham, NC, USA. Cancer Research (1988), 48(10), 2764-7. CODEN: CNREA8 ISSN: 0008-5472. Journal written in English. CAN 109:385 AN 1988:400385 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The effect and therapeutic consequences of buthionine (SR)-sulfoximine (BSO)-mediated depletion of glutathione in the human medulloblastoma-derived cell line TE-671, growing as s.c. xenografts in athymic nude mice, were examd. Administration i.p. to tumor-bearing mice of DL-BSO (2 doses at 12-h intervals; 5 mmol/kg) depleted the glutathione content of the xenografts to 25.7% of control. Administration of a 30 mM soln. of L-BSO in the drinking water for 96 h depleted the glutathione content to 17.4% of control.

Depletion of glutathione with these regimens increased the tumor growth delay over that produced by melphalan alone. These studies demonstrate the increased cytotoxicity of melphalan resulting from BSO-mediated depletion of glutathione in human medulloblastoma.

Answer 25:

Bibliographic Information

Xenografts in pharmacologically immunosuppressed mice as a model to test the chemotherapeutic sensitivity of human tumors. Floersheim, G. L.; Bieri, A.; Chiodetti, Nicole. Zent. Lehre Forsch., Kantonssp., Basel, Switz. International Journal of Cancer (1986), 37(1), 109-14. CODEN: IJCNAW ISSN: 0020-7136. Journal written in English. CAN 104:81665 AN 1986:81665 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

A human tumor xenograft model using pharmacol. immunosuppressed mice was assessed for its suitability to test preclinically the sensitivity of colorectal carcinomas, bone sarcomas and melanomas against anticancer agents. Beside ionizing radiation, 14 cytotoxic drugs including 5-fluorouracil (5-FU) [51-21-8], dimethylmyleran (DMM) [55-93-6], cytosine arabinoside [147-94-4], cyclophosphamide [50-18-0], melphalan [148-82-3], mitomycin C [50-07-7], adriamycin [23214-92-8], bleomycin [11056-06-7], etoposide [33419-42-0], vinblastine [865-21-4], cisplatin [15663-27-1], procarbazine [671-16-9], DTIC [4342-03-4], and BCNU [154-93-8] were assayed. Ionizing radiation, 5-FU and DMM were also applied at LDs followed by bone-marrow rescue high-dose therapy. Four colon carcinomas responded poorly to most of the agents but one tumor displayed marked sensitivity to BCNU. LDs of radiation, 5-FU and DMM and cyclophosphamide and by an osteosarcoma to the latter drug. No strong effects were seen against melanomas. LDs of DMM induced the best regression of one colon carcinoma. In general, the superiority of high-dose therapy for solid human tumors compared to maximally tolerated doses was demonstrated. Individual carcinomas of the same type displayed different drug sensitivity.

Answer 26:

Bibliographic Information

Chemotherapy of subcutaneous and intracranial human medulloblastoma xenografts in athymic nude mice. Friedman, Henry S.; Schold, S. Clifford, Jr.; Bigner, Darell D. Med. Cent., Duke Univ., Durham, NC, USA. Cancer Research (1986), 46(1), 224-8. CODEN: CNREA8 ISSN: 0008-5472. Journal written in English. CAN 104:61637 AN 1986:61637 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The continuous human medulloblastoma cell line TE-671 was grown as s.c. and intracranial xenografts in athymic nude mice; tumor-bearing animals were treated with chemotherapeutic agents at the 10% LD. The xenografts were sensitive to melphalan [148-82-3], 1-(2-chloroethyl)-3-(2,6-dioxo-1-piperidyl)-1-nitrosourea [84930-24-5], and 5-azacytidine [320-67-2]. No consistent response could be demonstrated to 9-β-D-arabinofuranosyl-2-fluoroadenine 5'-monophosphate [75607-67-9], and no response to methylglyoxal bis(guanyl hydrazone) [459-86-9], N-trifluoroacetyladriamycin 14-valerate [56124-62-0], or to 1-β-D-arabinofuranosylcytosine [147-94-4] was obsd. Melphalan produced an increase in the median survival of mice bearing intracranial xenografts, whereas no response was seen to 1-(2-chloroethyl)-3-(2,6-dioxo-1-piperidyl)-1-nitrosourea or 5-azacytidine. This model will allow anal. of the chemotherapeutic profile of human medulloblastoma, and provides a means to differentiate cellular sensitivity and resistance from drug access to the intracranial site.

Answer 27:

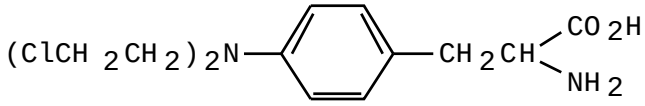
Bibliographic Information

Melphalan: a potential new agent in the treatment of childhood rhabdomyosarcoma. Houghton, Janet A.; Cook, Ruby L.;

Lutz, Pamela J.; Houghton, Peter J. Div. Biochem. Clin. Pharmacol., St. Jude Child. Res. Hosp., Memphis, TN, USA. Cancer Treatment Reports (1985), 69(1), 91-6. CODEN: CTRRDO ISSN: 0361-5960. Journal written in English. CAN 102:125192 AN 1985:125192 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Melphalan (I) [148-82-3] was evaluated against a series of 7 childhood rhabdomyosarcomas, each derived from a different patient and maintained in vivo as xenografts in immune-deprived mice. Six lines were derived from untreated tumors and 1 from a patient refractory to conventional therapy. At the max. tolerated dose (LD10) a single administration of melphalan caused complete regressions of advanced tumor in 6 of 7 lines, including xenografts derived from the refractory patient. This agent demonstrated activity over a broad range of doses, and was considerably more active than vincristine [57-22-7], cyclophosphamide [50-18-0], doxorubicin [23214-92-8], and dactinomycin [50-76-0] in the model.



I

Answer 28:

Bibliographic Information

Drug testing using a soft agar stem cell assay on patient and xenograft tumor material. Hanson, Jane; Coombs, Annie; Moore, John L. Radiobiol. Dep., Velindre Hosp., Whitchurch/Cardiff, UK. International Journal of Radiation Oncology, Biology, Physics (1984), 10(9), 1697-701. CODEN: IOBPD3 ISSN: 0360-3016. Journal written in English. CAN 102:17003 AN 1985:17003 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Fifty tumor samples from 10 different sites were studied. Over half were breast or ovarian tumors. Of the 27 that were considered suitable for cloning, 11 produced colony formation and 6 of these were drug tested. One ovarian granulosa cell tumor and its mouse xenograft (V7) were tested against several cytotoxic agents. During a period of 16 mo, sensitivity to cisplatin [15663-27-1] was relatively stable but sensitivity to vinblastine [865-21-4] was markedly changed when the original tumor cells and original cells stored in liq. N were compared with xenograft cells. These changes may be related to patient treatments prior to tumor sample collection. Gross histol. of original tumor and xenograft were similar. Chemosensitization in vivo of a breast xenograft (Hx99) to melphalan [148-82-3] by misonidazole [13551-87-6] was investigated. Misonidazole at a total dose of 0.5 g/kg given prior to melphalan (14 mg/kg) was an effective chemosensitizer.

Answer 29:

Bibliographic Information

Cell survival in four ovarian carcinoma xenografts following in vitro exposure to melphalan, cisplatin and cis-diammine-1,1-cyclobutanedicarboxylateplatinum(II) (CBDCA, JM8). Jones, Adrian C.; Wilson, Patricia A.; Steel, G. Gordon. Radiother. Res. Unit, Inst. Cancer Res., Sutton, UK. Cancer Chemotherapy and Pharmacology (1984), 13(2), 109-13. CODEN: CCPHDZ ISSN: 0344-5704. Journal written in English. CAN 101:183580 AN 1984:583580 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Four human ovarian carcinoma xenografts were established and maintained in immune-suppressed mice. Cells obtained from these

xenografts were exposed in vitro to melphalan [148-82-3], JM8 [41575-94-4], and cisplatin [15663-27-1]; cell survival following a 1-h exposure was measured using a soft-agar colony assay. A similar dose-response curve was obtained with melphalan for each of the 4 xenografts, despite previous treatment with an alkylating agent in two of the patients from whom the xenografts originated. Cell survival was also compared after JM8 and cisplatin exposure in each individual xenograft. It was found to be similar for each tumor when the concns. of JM8 used were 10-fold greater than those of cisplatin. Early clin. studies in which JM8 has been shown to be effective in the treatment of ovarian carcinoma support the view that xenograft tumors may have a role in phase-II screening of new cytotoxic agents.

Answer 30:

Bibliographic Information

Childhood rhabdomyosarcoma xenografts: responses to DNA-interacting agents and agents used in current clinical therapy. Houghton, Janet A.; Cook, Ruby L.; Lutz, Pamela J.; Houghton, Peter J. Div. Biochem. Clin. Pharmacol., St. Jude Child. Res. Hosp., Memphis, TN, USA. European Journal of Cancer & Clinical Oncology (1984), 20(7), 955-60. CODEN: EJCODS ISSN: 0277-5379. Journal written in English. CAN 101:163109 AN 1984:563109 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

A lab. model of childhood rhabdomyosarcoma (RMS) has been used to evaluate cytotoxic agents used in current clin. protocols, and DNA-reacting agents that have had either limited or no evaluation in this histiotype. Seven lines of RMS each derived from a different patient were grown as xenografts in immune-deprived mice, six of these being from specimens derived from previously untreated patients. Of the conventional' agents, vincristine [57-22-7] was the most effective. Of the other agents evaluated [L-phenylalanine mustard (L-PAM) [148-82-3], cis-dichlorodiammineplatinum (cis-DDP) [15663-27-1], mitomycin C [50-07-7] and 5-(3,3-dimethyl-1-triazeno)-imidazole-4-carboxamide (DTIC) [4342-03-4]], L-PAM caused complete regressions in six of seven lines, including those resistant to cyclophosphamide [50-18-0]. DTIC had marked activity in five tumors, and mitomycin C in three lines. Cyclophosphamide was active in five tumors, although efficacy was less marked in two lines in comparison to DTIC and mitomycin C.

Answer 31:

Bibliographic Information

Effect of five antineoplastic agents on tumor xenografts with different growth rates. Mattern, Juergen; Wayss, Klaus; Volm, Manfred. Dep. Exp. Pathol., German Cancer Res. Cent., Heidelberg, Fed. Rep. Ger. JNCI, Journal of the National Cancer Institute (1984), 72(6), 1335-9. CODEN: JJIND8 ISSN: 0198-0157. Journal written in English. CAN 101:103754 AN 1984:503754 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The effects of cyclophosphamide (Cy) [50-18-0], doxorubicin (Dx) [23214-92-8], cisplatin (DDP) [15663-27-1], melphalan (L-PAM) [148-82-3], and vincristine (VCR) [57-22-7] on various human and animal tumor lines with different growth rates, growing as xenografts in NMRI (nu/nu) mice, were studied. Two types of response were obsd.: For Cy and Dx, the response of the xenografts was neg. correlated with tumor vol. doubling time (TD), indicating that rapidly growing tumors were more sensitive to these drugs than were slowly growing tumors. For DDP, L-PAM, and VCR, the effects were pos. correlated with the TD, indicating that slowly growing tumors were more sensitive to these drugs than rapidly growing tumors. The data are discussed in relation to the effects of the drugs on proliferating and nonproliferating cells obtained with other cell lines.

Answer 32:

Bibliographic Information

Induced and inherent resistance to alkylating agents in human small-cell bronchial carcinoma xenografts. Berman, R.; Steel, G. G. Radiother. Res. Unit, Inst. Cancer Res., Sutton, UK. British Journal of Cancer (1984), 49(4), 431-6. CODEN: BJCAAI ISSN: 0007-0920. Journal written in English. CAN 100:203254 AN 1984:203254 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Inherent and induced resistance was investigated in human small-cell lung cancer xenografts. Specimens from patients were established in immune suppressed mice; the sensitivity of the xenografts to cyclophosphamide [50-18-0], MeCCNU [13909-09-6], and melphalan [148-82-3] was detd. Clin. chemosensitivity data were available in 2 cases and inherent differences in sensitivity were noted both in the xenografts and clin. Radioactively-labeled melphalan uptake studies were performed with these 2 xenografts. A no. of different strategies to induce resistance were explored. Only 1 method proved to be successful and in only 1 of the xenografts; this was with cyclophosphamide. The induced resistant line was characterized in terms of the time course of its prodn., the degree of induced resistance, the growth rate, the cross-resistance pattern and stability of the phenotype; the possibility of altered antigenicity was also examd.

Answer 33:

Bibliographic Information

Misonidazole enhancement of the action of BCNU and melphalan against human melanoma xenografts. Clutterbuck, R. D.; Millar, J. L.; McElwain, T. J. Div. Phys., Inst. Cancer Res., Sutton/Surrey, UK. American Journal of Clinical Oncology (1982), 5(1), 73-8. CODEN: AJCODI ISSN: 0277-3732. Journal written in English. CAN 96:174042 AN 1982:174042 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The effects of combinations of BCNU [154-93-8] and misonidazole [13551-87-6], and melphalan [148-82-3] and misonidazole on growth delay in 2 human malignant melanoma xenograft lines grown in immune-deprived mice were investigated. Misonidazole on its own had no effect on the growth of these tumors, but combinations of BCNU-misonidazole and melphalan-misonidazole produced greater tumor growth delays than those produced by the cytotoxic drugs alone. This was accompanied by increased wt. loss. Misonidazole in combination with melphalan also increased hemopoietic stem cell toxicity, but in the case of BCNU there was no enhancement of bone marrow toxicity at the dose chosen for tumor expts.

Answer 34:

Bibliographic Information

Chemotherapy of human breast-carcinoma xenografts. Bailey, M. J.; Gazet, J. C.; Smith, I. E.; Steel, G. G. Inst. Cancer Res., Sutton/Surrey, UK. British Journal of Cancer (1980), 42(4), 530-6. CODEN: BJCAAI ISSN: 0007-0920. Journal written in English. CAN 94:95754 AN 1981:95754 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Sensitivities were varied for 5 lines of human breast carcinoma xenografts, grown and passaged in immune-suppressed mice, to cyclophosphamide [50-18-0], methotrexate [59-05-2], 5-fluorouracil [51-21-8], adriamycin [23214-92-8], vincristine [57-22-7], and melphalan [148-82-3], alone and in combination. The most effective single agent or combination differed for each tumor. This system may be useful for testing new cytotoxic agents and predicting clin. chemotherapy response.

Answer 35:

Bibliographic Information

A comparison of the chemosensitivity of a primary tumor and its metastases using a human tumor xenograft. Selby, P. J.; Thomas, J. M.; Peckham, M. J. Div. Biophys., Inst. Cancer Res., Sutton/Surrey, UK. European Journal of Cancer (1965-1981) (1979), 15(12), 1425-9. CODEN: EJCAAH ISSN: 0014-2964. Journal written in English. CAN 92:104460 AN 1980:104460 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Clonogenic cell survival curves were constructed for melphalan [148-82-3] treatment of primary and secondary tumors of a human xenograft in immune deprived mice. The small metastases were more sensitive to melphalan than the larger primary tumors. Expts. with radiolabeled melphalan suggested that the greater sensitivity of the small tumors was due to better drug penetration.

Answer 36:

Bibliographic Information

Effect of serial passage in nude athymic mice on the growth characteristics and chemotherapy responsiveness of 13762 and R3230AC mammary tumor xenografts. Bogden, Arthur E.; Kelton, Diane E.; Cobb, William R.; Gulkin, Theodore A.; Johnson, Randall K. Dep. Tumor Biol. Exp. Cancer Ther., Mason Res. Inst., Worcester, MA, USA. Cancer Research (1978), 38(1), 59-64. CODEN: CNREA8 ISSN: 0008-5472. Journal written in English. CAN 88:182251 AN 1978:182251 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Serial passage of the R3230AC and 13762 rat mammary adenocarcinomas for 20 generations in nude athymic mice revealed changes in biol. and chemotherapy response characteristics indicating a tumor-host relationship that questions long-term stability of the tumor xenograft-nude mouse test system. Unresponsiveness to L-phenylalanine mustard (NSC 8806), of the R3230AC tumor, remained stable, but attempts to reestablish progressive growth in previously syngeneic hosts were unsuccessful. Responsiveness to L-phenylalanine mustard, a characteristic of the 13762 tumor marked by oncolysis and many complete remissions in syngeneic hosts, was significantly reduced with no complete remissions after the tenth passage. When tumors were reestablished in syngeneic hosts, tumor growth pattern and responsiveness to L-phenylalanine mustard returned to normal by the second passage. Clearly definable acinar structures typical of the R3230AC and 13762 adenocarcinomas were markedly reduced in the R3230AC and disappeared in the 13762 after serial passage in nude mice. Acini were still absent from the 13762 tumor after being reestablished for 3 passages in syngeneic females. The chromosomal modes of both tumors were unchanged. These results stress the need for careful monitoring of growth and of biol. and chemotherapeutic response characteristics and for periodic replacement of tumor lines to assure long-term stability of the tumor xenograft-nude mouse test system.

Answer 37:

Bibliographic Information

Phase II testing of melphalan in children with newly diagnosed rhabdomyosarcoma: a model for anticancer drug development. Horowitz M E; Etcubanas E; Christensen M L; Houghton J A; George S L; Green A A; Houghton P J Department of Hematology-Oncology, St. Jude Children's Research Hospital, Memphis, TN Journal of clinical oncology : official journal of the American Society of Clinical Oncology (1988), 6(2), 308-14. Journal code: 8309333. ISSN:0732-183X. (CLINICAL TRIAL); Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T); (RESEARCH SUPPORT, U.S. GOV'T, P.H.S.) written in English. PubMed ID 3276826 AN 88117656 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

We describe events that led to successful testing of melphalan, one of the nitrogen mustard compounds, in children with newly diagnosed, poor-risk rhabdomyosarcoma (RMS). Preclinical studies with xenografts of human RMS, growing in the flanks of immune-deprived mice, had indicated superior oncolytic activity by melphalan compared with other agents commonly used to treat this tumor. However, in a conventional phase II trial, melphalan failed to produce partial responses in 12 of 13 heavily pretreated patients with recurrent tumors. Subsequent comparison of the drug's pharmacokinetics in mice and patients indicated that its poor clinical performance was not the result of interspecies differences in drug disposition. Therefore, we elected to retest melphalan in untreated patients, before they were enrolled in a phase III study. Of 13 children who received the drug for 6 weeks, ten had partial responses, confirming the significant antitumor activity seen in the xenograft system. These findings illustrate the inherent limitations of phase II drug trials in previously treated patients and suggest a useful paradigm for the development of antineoplastic drugs.

Answer 38:

Bibliographic Information

The combination of melphalan with prednisolone. Anti-tumor effect and normal tissue toxicity in laboratory systems. Selby P J; Millar J L; Phelps T A; Gordon M Y; Wilkinson R; McElwain T J Cancer chemotherapy and pharmacology (1981), 6(2), 169-73. Journal code: 7806519. ISSN:0344-5704. Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 7307234 AN 82070646 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

The effect of prednisolone upon the therapeutic index of melphalan has been studied in a variety of laboratory systems. The anti-tumour action of melphalan was assessed for a human melanoma xenograft growing in immune-deprived mice, clonogenic cell survival and tumour growth delay being used as end-points. Normal tissue toxicity was assessed for human bone marrow colony-forming units, murine bone marrow colony-forming units, murine gastrointestinal crypt microcolony-forming cells, and mouse survival. Prednisolone had no anti-tumour effect when given alone, but increased the anti-tumour effect of melphalan significantly. No increase in the toxicity of melphalan to marrow or gut colony-forming cells could be demonstrated. However, mouse survival was significantly lower after treatment with the combination than with melphalan alone. This study supports the view that steroids may enhance the anti-tumour effect of some alkylating agents, but this may be at the expense of increased normal tissue toxicity in some circumstances.